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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,327	09/03/1999	SARAH ANNE ROBERTSON	A20-005	2475

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,327	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- *Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).*
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/11/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-59,64-71,79,81,83,86-93 and 98-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-59, 64-71, 79, 81, 83, 86-93 and 98-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ *Copies of the certified copies of the priority documents have been received in this National Stage* application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ *Notice of Draftsperson's Patent Drawing Review (PTO-948)*
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ *Notice of Informal Patent Application (PTO-152)*
6) ☐ Other: .

DETAILED ACTION

1. Claims 50-59, 64-71, 79, 81, 83, 86-93 and 98-104 are pending.

2. In view of the declaration by David Clark and amendment filed 9/16/03, the following objection and rejections remain.

3. The drawings, filed on 9/3/99, stand not in compliance with 37CFR 1.84(a). Please see attached PTO 948 mailed 3/14/01. Appropriate correction is required. It is noted that formal drawings will be submitted at a later time prior to or at payment of the issue fee. It is noted that Applicants will submit them in due course but no later than at the time of payment of the issue fee.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 50-59, 64-71, 79, 81, 83, 86-93 and 98-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diminishing DTH immune response to sperm antigen in a prospective mammalian mother to sperms of a prospective father to alleviate implantation failure, said method comprising administering said prospective mother to said sperm antigens of said prospective father and to substantially purified TGFβ, said method leading to tolerance to said sperm antigens and alleviation of said infertility condition, **does not** reasonably provide enablement for a method of treating *any* infertility condition such as miscarriage, spontaneous abortion, pre-eclampsia, and early embryonic loss in any mammalian prospective mother comprising exposing the prospective mother to (1) *any* one or more sperm antigens or any MHC Class I antigens of the prospective father and a substantially purified TGFβ such as TGFβ2, TGFβ3 and activin thereby to induce tolerance to said antigen or antigens wherein said MHC Class I antigen is one which is present on leukocytes or in seminal plasma of said prospective father as set forth in claims 50-59, 64-71, 79, 81, 83, 86-93 and 98-104. The specification disclosure is insufficient to

enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses only a method of diminishing DTH immune response to sperm antigen in a prospective mother such as mice to **sperm antigen** (antigens on the sperm) and MHC class I by co administering sperm antigen in the form of the prospective father's ejaculate and rTGFβ1 together before attempted conception (see page 7 line 35, Fig 9 of specification) or administering TGFβ after intercourse (See page 8, line 4-5) to induce tolerance and for alleviate the symptoms of infertility conditions. The specificity of TGFβ to be co-administered with the male antigens is at present not entirely clear. and because TGFβ 1 is thought to be responsible whereas TGFβ 2,3 are less important. It is more likely that TGFβ1 is to be used (page 9, line 7-9). The specification merely shows the effect of porcine TGFβ2, and activin on GM-CSF production by uterine epithelial cells in vitro (Figure 4). However, GM-CSF initiates an influx and activation of inflammatory cells (page 22).

The specification does not teach how to treat any infertility conditions such as miscarriage, spontaneous abortion, pre-eclampsia, and early embryonic loss in any mammalian prospective mother such as human comprising exposing the prospective mother to *any* one or more sperm antigens, any MHC Class I antigens present on leukocytes or in seminal plasma of the prospective father and a substantially purified TGFβ2, TGFβ3 or activin for the following reasons. The specification discloses "TGFβ 2,3 are less important (page 9, lines 7-9). First, There is insufficient guidance as to the structure such as the specific amino acid sequence of any sperm antigens or any MHC class I antigen in seminal plasma of any prospective father for the claimed method. Applicant has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the sperm

antigen(s), the antigens in seminal plasma other than antigen already on the sperm or leukocyte from the prospective father.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Second, the specification discloses "It is more likely that TGFβ1 is to be used" for induce immune tolerance to sperm antigen or MHC class I antigen on sperm of a prospective father". Third, the specification merely shows the effect of porcine TGFβ2, and activin on GM-CSF production by uterine epithelial cells *in vitro* (Figure 4). However, GM-CSF initiates an influx and activation of inflammatory cells (page 22). It is not clear the role of increasing GM-CSF production in vitro in relation to the induction of maternal tolerance to paternal antigen by immunizing the female with the sperm of the prospective father in the present of TGFβ1. Third, there is insufficient *in vivo* working example demonstrating that any TGFβ such as TGFβ2, TGFβ3 or activin could treat *any* infertility condition such as miscarriage, spontaneous abortion, pre-eclampsia given that only neutralizing antibody to TGFβ1 could block GM-CSF production *in vitro* (Figures 1, 2, page 21 of specification).

Mason *et al*, of record, teach that even one amino acid substitution such as cysteine for alanine (there were 9 of them in total) of activin A, which is a member of TGFβ family fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular) or loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) or loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach that the equivalent in TGFβ1 in which the cysteine residue corresponding to residue 77 when changed to a serine residue, the resulting secreted monomer has no bioactivity (See page 330, column 1, first paragraph, in particular).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 6/14/01 and 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 75 to 77 have been canceled; the claims no longer encompass substitution, deletion, or addition mutants or peptide fragments of TGFβ. (2) Infertility in humans and mice was not ascribable in 1997 to lack of "immunological tolerance" to paternal antigen wherein maternal CTLs were prevented from recognizing and rejecting allogeneic embryos. It was the understanding of a person skilled in the art in 1997 that embryo failure was related to NK cells which lack T cell receptors for antigens such as paternal antigens. In 1997, non-antigen-specific NK cells were not considered to be part of the antigen-specific immune system. Immunological tolerance refers to an alteration of antigen-specific immune function, not non-specific cells such as NK cells. The CTL assay used by Clark et al was merely a convenient in vitro assay for immunosuppressive molecule such as TGFβ.

However, the amended claims still recite any sperm antigens, any MHC class I antigen in seminal plasma of prospective father.

The specification does not teach how to treat any infertility conditions such as miscarriage, spontaneous abortion, pre-eclampsia, and early embryonic loss in any mammalian prospective mother such as human comprising exposing the prospective mother to *any* one or more sperm antigens, any MHC Class I antigens present on leukocytes or in seminal plasma of the prospective father and a substantially purified TGFβ2, TGFβ3 or activin for the following reasons. The specification discloses that "TGFβ 2,3 are less important (page 9, lines 7-9). First, There is insufficient guidance as to the structure such as the specific amino acid sequence of any sperm antigens or any MHC class I antigen in seminal plasma of any prospective father for the claimed method. Applicant has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the sperm

antigen(s), the antigens in seminal plasma other than antigen already on the sperm or leukocyte from the prospective father.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the indefinite number of undisclosed "antigens", there is insufficient working example demonstrating that any antigen is effective for induction of tolerance as a method of treating any infertility condition such as miscarriage, spontaneous abortion, pre-eclampsia in any mammalian prospective mother. It is unpredictable which undisclosed antigens would be useful for induction of tolerance, in turn, for a method of alleviating the symptoms of infertility condition. Second, the specification discloses "It is more likely that TGFβ1 is to be used" for induce immune tolerance to sperm antigen or MHC class I antigen on sperm of a prospective father". Third, the specification merely shows the effect of porcine TGFβ2, and activin on GM-CSF production by uterine epithelial cells *in vitro* (Figure 4). However, GM-CSF initiates an influx and activation of inflammatory cells (page 22). It is not clear the role of increasing GM-CSF production in vitro in relation to the induction of maternal tolerance to paternal antigen by immunizing the female with the sperm of the prospective father in the present of TGFβ1. Third, there is insufficient *in vivo* working example demonstrating that any TGFβ such as TGFβ2, TGFβ3 or activin could treat *any* infertility condition such as miscarriage, spontaneous abortion, pre-eclampsia given that only neutralizing antibody to TGFβ1 could block GM-CSF production *in vitro* (Figures 1, 2, page 21 of specification). The specification as filed discloses only that Bald/k mice were given intra-uterine infusions of sperm from Balb/c(H-2d) males together with TGFβ1. These mice were not able to reject paternal MHC antigen bearing tumor cells (induction of maternal tolerance to paternal antigen). However, pregnancy is a form of immune tolerance.

In contrast to Applicant's argument that infertility in humans and mice was not ascribable in 1997 to lack of "immunological tolerance" to paternal antigen wherein maternal CTLs were prevented from recognizing and rejecting allogeneic embryos, the teachings of the '825 patent issued in 1995 would suggest otherwise. In fact, TGFβ is found in the immunologically privileged sites such as the anterior chamber of the eyes

and fetoplacenta within the pregnant uterus and has been shown to delay or prevent organ rejection (immune tolerance) as evidence in the Ruscetti et al (Annals New York Academy of Sciences 685:488-500, especially page 494-495, 1994; PTO 1449). Further, there is no evidence that the method in the instant claims would differ in an unexpected manner from those described in the references. In the absence of unexpected results, applicant's arguments were not found persuasive.

6. Claims 50-59, 64-71, 79, 81, 83, 86-93 and 98-104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method of alleviating symptoms of an infertility condition in any mammalian prospective mother comprising exposing the prospective mother to a method of treating *any* infertility condition such as miscarriage, spontaneous abortion, pre-eclampsia, and early embryonic loss in any mammalian prospective mother comprising exposing the prospective mother to (1) *any* one or more sperm antigens or any MHC Class I antigens of the prospective father and a substantially purified TGFβ such as TGFβ2, TGFβ3 and activin thereby to induce tolerance to said antigen or antigens wherein said MHC Class I antigen is one which is present on leukocytes or in seminal plasma of said prospective father as set forth in claims 50-59, 64-71, 79, 81, 83, 86-93 and 98-104.

The specification discloses only a method of eliciting an immune response in a prospective mother to sperm antigens (antigens on the sperm) and MHC class I by co administering sperm antigens in the form of the prospective father's ejaculate and TGFβ together before attempted conception (see page 7 line 35, Fig 9 of specification) or administering TGFβ after intercourse (See page 8, line 4-5) to induce tolerance and for alleviate the symptoms of infertility conditions. The specification discloses on page 8 at line 7 that the nature of the relevant surface antigens is not entirely clear but will presumably be those that are particularly antigenic and prominent either on the sperm or on the conceptus. The most likely candidates are MHC antigens and more preferably MHC class I. The surface antigens from the male parent may include leukocytes, the antigens may also be presented in biological fluids such as seminal plasma.

However, the term "antigen" without the specific amino acid sequence and SEQ ID NO has no structure, much less function, in turn, would be useful as a method for treating *any* infertility condition in any mammalian prospective mother. With the exception of the specific sperm antigen and the specific TGFβ1 mentioned above, there is insufficient written description about **the structure associated with function** of *any MCH class I* antigens in seminal plasma. The specification discloses only MHC class I antigen associated with the sperm or leukocytes. Applicant has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the antigen or antigens in seminal plasma. Further, there is inadequate written description about the use of TGFβ2, TGF3, and activin for the claimed method of treating any infertility condition such as miscarriage, spontaneous abortion, pre-eclampsia, early embryonic loss, and implantation failure.

Given the lack of a written description of any additional species of TGFβ and antigen used for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 9/16/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 75-77, 84 and 85 have been deleted. (2) amended claim 50 specifies that the TGFβ is selected from the group consisting of TGFβ1, TGFβ2, TGFβ3 and activin.

However, the amended claims still recite any antigen present in the seminal plasma for the claimed method of treating any infertility condition.

The specification discloses only a method of eliciting an immune response in a prospective mother to sperm antigens (antigens on the sperm) and MHC class I by co administering sperm antigens in the form of the prospective father's ejaculate and TGFβ together before attempted conception (see page 7 line 35, Fig 9 of specification) or administering TGFβ after intercourse (See page 8, line 4-5) to induce tolerance and for alleviate the symptoms of infertility conditions. The term "antigen" without the specific

amino acid sequence and SEQ ID NO has no structure, much less function, in turn, would be useful for a method for treating *any* infertility condition in any mammalian prospective mother.

With the exception of the specific sperm antigen and the specific TGFβ1 mentioned above, there is insufficient written description about **the structure associated with function** of *any MCH class I* antigens in seminal plasma. The specification discloses only MHC class I antigen associated with the sperm or leukocytes. Applicant has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the antigen or antigens in seminal plasma. Further, there is inadequate written description about the use of TGFβ2, TGF3, and activin for the claimed method of treating any infertility condition such as miscarriage, spontaneous abortion, pre-eclampsia, early embryonic loss, and implantation failure. In fact, the specification discloses "It is more likely that TGFβ1 is to be used" for induce immune tolerance to sperm antigen or MHC class I antigen on sperm of a prospective father".

Given the lack of a written description of any additional species of TGFβ and antigen used for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 50-59, 64-67, 70, 79, 81, 86, 89, 90, 92-93, and 98-104, are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; PTO 1449) in view of Clark *et al* (of record, Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892).

The '825 patent teaches a method of treating infertility such as early embryonic loss, implantation failure, spontaneous abortion and preeclampsia associated with IVF by administering TGFβ, such as TGFβ1, TGFβ2, TGFβ3, and TGFβ4 (See column 5, line 9-11, in particular) along with antigens such as ovum, **sperm** on the surface or conceptus into the reproductive track (genital mucosal surface) of the a female to bolster the chances that a pregnancy will be sustained by increasing the success rate of implantation (See column 5 line 9-12, claim 4 of '825 patent, in particular). The reference TGFβ may be administered either before, after or simultaneously with the male antigens such sperms of the prospective father which are known to express MHC class I molecule on the surface (sperm antigens) and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21, in particular). The reference TGFβ or analog may be administered by intravenous injection (systemic contact), patch, and gels that are slow release (See column 5, line 1-2; column 6, line 45-55, in particular). The '825 patent further teaches a method of diagnosing or testing the presence of active and/or immunological TGFβ in female or diagnosing mammals with infertility due to inadequate TGFβ (See column 6, line 8-16, column 3, lines 59-65, in particular). The reference method also can be used in conjunction with assisted reproduction such as IVF (See column 3 lines 66 bridging column 4, lines 6, in particular). The '825 patent teaches

that TGFβ stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular).

The claimed invention as recited in claim 50 differs from the teachings of the reference only that the method of eliciting symptoms of an infertility condition in a mammalian mother comprising exposing the prospective mother to one or more sperm antigens or MHC Class I antigens of a prospective father to induce tolerance to said antigen or antigens wherein said MHC class I antigen is one which is present on leukocytes of said prospective father.

The claimed invention as recited in claim 55 differs from the teachings of the reference only that the TGFβ and the one or more antigens are administered at one site.

The claimed invention as recited in claim 56 differs from the teachings of the reference only that TGFβ and the MHC Class I antigen or antigens are each administered at a first site and a different site respectively.

The claimed invention as recited in claim 66 differs from the teachings of the reference only that the one or more antigens are presented in purified or semi-purified form.

The claimed invention as recited in claim 67 differs from the teachings of the reference only that the method include inert or adjuvant carriers.

The claimed invention as recited in claim 79 differs from the teachings of the reference only that the TGFβ is administered in its active form.

The claimed invention as recited in claim 86 differs from the teachings of the reference only that the human beings are being treated and the exposure to TGFβ and male antigen is a multiple exposure.

The claimed invention as recited in claim 98 differs from the teachings of the reference only that the method wherein infertility condition is a condition associated with maternal immune response to a conceptus in a mammalian prospective mother.

Clark *et al* teach that bioactive TGFβ is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Chaouat *et al* teach that immunizing female with the male leukocyte which carried the paternal MHC class I haplotype in a carrier such as PBS can lead to an increase protection during pregnancy (See abstract, Materials and Methods, in particular).

Chaouat *et al* teach the protection is associated with active suppression against maternal cell-mediated immunity in the form of tolerance (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the sperm antigen in the method of treating infertility as taught by the '852 patent for the MHC class I antigen on leukocyte as taught by Chaouat el al for a method of treating infertility as taught by the '825 patent thereby to induce tolerance (immunesuppression) as taught by Clark et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '825 patent teaches that TGFβ stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular). Clark *et al* teach bioactive TGFβ is known to suppress the generation of cytotoxic T cells in vitro and has immunosuppressive activity that leads to induction of tolerance in vivo during the first trimester pregnancy in humans (See abstract, in particular). Chaouat *et al* teach that immunizing female with the male leukocyte which carried the paternal MHC class I haplotype can lead to protection of fetus from maternal cell-mediated immunity (See Abstract, in particular). Claims 55-56 are included in this rejection because the recitation of administering systemically TGFβ and one or more antigens or TGFβ and one or more antigens each administered at a first site and a different site is an obvious variation of the teaching of the '825 patent since the '825 patent teaches that TGFβ can be administered simultaneously, before or after the antigen and the sites of administration is within the purview of one ordinary skilled in that art at the time the invention was made. Claim 79 is included in this rejection because the recitation of active form is within the teachings of '825 patent because administering TGFβ and antigens lead to increase the success rate of implantation, which is the active form of TGFβ (See entire document, Claims of 825 patent, in particular). Claim 86 is included in this rejection because the recitation of multiple exposure to TGFβ and male antigen is within the purview of one of ordinary skilled in the art based on the teachings of the '825 patent. Claim 98 is included in this rejection because infertility condition is inherently associated with maternal immune response as evidence by the teaching of Chaouat *et al*, who teaches that the protection is

associated with active suppression against maternal cell-mediated immunity in the form of tolerance (See Abstract, in particular).

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 9/11/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) The Clark et al reference discloses the up-regulation of release in vitro of non-conventional TGFβ from CD56+ cells obtained from deciduas of human first trimester pregnancy, the non-conventional TGFβ was assayed in vitro using mouse CTL generation. However, the results of this assay alone do not indicate or suggest the biological function of non-conventional TGFβ. The Clark et al reference does not teach that the non-conventional TGFβ in vivo has immunosuppressive activity in vivo during the first trimester of pregnancy. (2) Infertility in humans and mice was not ascribable in 1997 to lack of "immunological tolerance" to paternal antigen wherein maternal CTLs were prevented from recognizing and rejecting allogeneic embryos. It was the understanding of a person skilled in the art in 1997 that embryo failure was related to NK cells which lack T cell receptors for antigens such as paternal antigens. In 1997, non-antigen-specific NK cells were not considered to be part of the antigen-specific immune system. Immunological tolerance refers to an alteration of antigen-specific immune function, not non-specific cells such as NK cells. The CTL assay used by Clark et al was merely a convenient in vitro assay for immunosuppressive molecule such as TGFβ. (3) Even if Clark et al did teach that TGFβ has immunosuppressive activity in vivo, this does not equate to or even foreshadow immune tolerance. Suppression of antigen-non-specific NK cells related to spontaneous abortion is not "immune tolerance". This contrast with induction of tolerance as it applies to Chaouat et al because in this murine model, an active response to paternal antigens was required to suppress NK cell activity. (4) One would not have expected that administering a conventional TGFβ isoform would prove beneficial in preventing infertility or as now claims define a method of treating an infertility condition in a mammalian prospective mother. (5) Chaoaut discloses immunizing a female CBA/J mouse with BALB/c leukocytes from spleen which carried paternal DBA/2 MHC class I antigen. Immunity elicited by administering paternal strain DBA/2 spleen leukocytes was not protective. It was not necessary to use spleen cells from male BALB/c mice; BALB/c spleen cells from female mice were effective in inducing the immunity. Based on the teachings of Chaouat, one would not have expected that immunizing with paternal

leukocytes would prove beneficial in treating an infertility condition. In fact, there were a number of studies (Exhibit A-C) published before the priority date of the present application which showed that immunizing human females with paternal antigen per se had not proven beneficial in treating an infertility condition in contrast to the murine studies of Chaouat et al. There was uncertainty as to whether "immunizing with paternal antigen" to treat infertility condition was efficacious. In fact, study by Ober et al (Exhibit D), even after the present filing date, show that immunizing women with paternal lymphoid cells alone did not improve pregnancy outcome in infertility. (6) Chaouat reference does not provide any motivation to combine its teachings with those of Feinberg and Clark in order to arrive at the applicant's invention as claimed. (7) A person of ordinary skill in the art would not have been motivated to combine the disclosures of these references in order to arrive at the invention as now claimed.

In response to Applicant's argument that the Clark et al reference does not teach that the non-conventional TGFβ, assuming it is TGFβ2, in vivo has immunosuppressive activity in vivo during the first trimester of pregnancy, however, the '825 patent teaches conventional TGFβ (TGFβ1) as well as non-conventional TGFβ such as TGFβ2, and TGFβ3 (See column 5, line 9-11, in particular) in combination with sperm antigens for treating infertility (See column 5 line 9-12, claim 4 of '825 patent, in particular). Further, Clark et al teach that TGFβ2 has immunosuppressive activity (See entire document). The '825 patent teaches TGFβ such as TGFβ2 treatment improved survival of the fetus following implantation.

In response to Applicant's argument that suppression of antigen-non-specific NK cells related to spontaneous abortion is not "immune tolerance", the '825 patent teaches a method of treating infertility by administering sperm antigen of the prospective father and TGFβ such as TGFβ2, and TGFβ3 to the prospective mother. In fact, the claimed method steps is the same as the method steps in the '825 patent (See column 6, line 48 bridging column 7, lines 1-20, claim 4 of '825 patent, in particular). The '825 patent teaches that TGFβ may be administered either before, after or simultaneously with the male antigens such as the sperms of the prospective father which are known to express MHC class I molecule on the surface and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21). The injection of

TGFβ to the prospective mother inherently induces maternal immune tolerance to paternal sperm antigen.

In contrast to Applicant's argument that infertility in humans and mice was not ascribable in 1997 to lack of "immunological tolerance" to paternal antigen wherein maternal CTLs were prevented from recognizing and rejecting allogeneic embryos, Chaouat *et al* teach that immunizing female with the male leukocyte which carried the paternal MHC class I haplotype in a carrier such as PBS can lead to an increase protection during pregnancy (See abstract, Materials and Methods, in particular). Chaouat *et al* teach the protection is associated with active suppression against maternal cell-mediated immunity in the form of tolerance (See Abstract, in particular). Cell mediated immunity includes CTLs and NK immunity. Although Chaouat et al does not teach the use of TGFβ for treating infertility, the '825 patent teaches the use of TGFβ and sperm antigen for treating infertility. Further, the immunological tolerance or immnuosuppressive effect of TGFβ is widely known as evidence by the teachings of Clark and others at the time the invention was made. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991).

In response to Applicants' argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., maternal CTLs were prevented from recognizing and rejecting allogeneic embryos) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, none of the claims recite "T-cell tolerance".

In contrast to applicant's assertion that one would not have expected that administering a conventional TGFβ isoform would prove beneficial in treating an infertility condition in a mammalian prospective mother, the '582 patent teaches treating infertility using conventional TGFβ isoform such as TGFβ1, TGFβ2, TGFβ3 (See column 5, line 10, in particular).

In contrast to Applicants' argument that was uncertainty as to whether "immunizing with paternal antigen" to treat infertility condition was efficacious, the '582

patent teaches treating infertility by immunizing paternal antigen such as sperm with TGFβ (See discussion above). Note, amended Claim 50 still recites a method of treating an infertility condition using one or more sperm antigens of a prospective father and TGFβ.

10. Claims 66-67 and 71 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-59, 64-67, 70, 79, 81, 86, 89, 90, 92-93, and 98-104 and further in view of Harlow *et al* (in A Laboratory Manual, Cold Spring Harbor Laboratory, page 61, 1988; PTO 892), World Health Organization (in World Health Organization Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction, Cambridge University Press, NY 1987, PTO 892) and Martin-Villa *et al* (Biol Reprod 55(3): 620-9, Sept 1996; PTO 892).

The combined teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claims 66-67 differs from the teachings of the references only by the recitation that one or more antigens are presented in purified or semi-purified form.

The claimed invention as recited in claim 71 differs from the teachings of the references only by the recitation that the exposure of one or more antigens is to the prospective mother's genital tract in the form of the prospective father's ejaculate, and the level of exposure is determined by the cell count and antigenic density on the surface of such cells.

Harlow *et al* teach a simple method of purifying any protein antigen by polyacrylamide gels electrophoresis (See page 61, in particular). Harlow *et al* having pure antigen provides the best case for the production of antibodies.

The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate (See page 5, page 9, Counting the spermatozoa, in particular) and various methods of determining male infertility.

Martin-Villa *et al* teach a method of purifying sperm and determining antigen density such as HLA on cell surface using double labeling cytofluorometry and relevant

antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA (See entire document, Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to purify antigen as taught by Harlow *et al* using the antigens from the sperm or conceptus as taught by the '285 patent or the semi-purify sperm antigens from the ejaculate by washing and counting as taught by the WHO Laboratory Manual for the Examination of Human Semen or the purified human spermatozoa from the prospective father 's ejaculate and determining the antigen density by double labeling cytofluorometry and relevant antibody as taught by Martin-Villa *et al* to determine the levels of antigen prior to exposing the prospective mother's genital tract to one or more antigens to induce immune tolerance to the antigen(s) of the prospective father for a method of eliciting an immune reaction and alleviation of symptoms of infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Harlow *et al* teach purifying any protein antigen by polyacrylamide gels electrophoresis is a simple method (See page 61, in particular). The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate is useful for (See page 5, page 9, Counting the spermatozoa, in particular) determining male infertility. Martin-Villa *et al* teach a method of purifying sperm and determining antigen density such as HLA on cell surface using double labeling cytofluorometry using relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA, as one of the indicator for male fertility (See entire document, Abstract, in particular).

11. Claim 83 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark et al (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-59, 64-67, 70, 79, 81, 86, 89, 90, 92-93, and 98-104 and further in view of Grainger *et al* (Nat Med 1(9): 932-7, Sep1995; PTO 892).

The combined teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 83 differs from the teachings of the references only by the recitation that the method of treating includes administration of plasmin as to increase the level of active TGFβ.

Grainger *et al* teach transforming growth factor beta 1 (TGF-beta 1) is a platelet-derived cytokine and human whole platelets is a rich source of inactive TGF-beta 1, which can be activate by plasmin (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the active TGF beta as taught by the '825 patent for the unpurified form using a biological source rich in TGFβ such as the platelets along with plasmin to activate the inactive form of TGFβ as taught by Grainger *et al* for a method of eliciting an immune reaction in a prospective mammalian mother comprising exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGFβ, said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by '825 patent, Clark *et al*, and Chaouat *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Grainger *et al* teach platelet is a rich of inactive TGFβ and which can be activate by plasmin (See abstract, in particular).

12. Claim 92 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Clark *et al* (Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Chaouat *et al* (of record, J Immunology 134(3): 1594-8, March 1985; PTO 892) as applied to claims 50-62, 64-67, 70, 73, 77, 79, 81, 89, 90, 92 and 93 and further in view of Heidenreich *et al* (Am J Reprod Immunol 31(2-3): 69-76, Mar-Apr 1994; PTO 892).

The combined teachings of the '825 patent, Clark *et al*, and Chaouat *et al* have been discussed supra.

The claimed invention as recited in claim 92 differs from the teaching of the references only by the recitation that the method includes testing whether anti-sperm antibodies exist.

Heidenreich *et al* teach a method of detecting anti-sperm antibody in infertile male using a highly sensitive and reproducible ELISA assay (See abstract, in particular). The reference assay synchron ELISA (Synelisa) is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the step of diagnosing whether anti-sperm antibodies exist using the assay as taught by Heidenreich *et al* with the method of treating infertility by administering TGFβ and male antigens as taught by the '825 patent, Clark *et al,* and Chaouat *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Heidenreich *et al* teach anti-sperm antibody is associated with male infertility and the reference assay is useful for is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

13. The following new ground of objection is necessitated by the amendment filed 9/19/03.

14. Claims 98-104 are objected to because "A method" should have been "The method" for dependent claims.

15. Claims 68-69, 87-88 and 91 stand free of art.

16. No claim is allowed.

17. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

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